



Regroupement des Gynécologues Oncologues du Québec

18E CONGRÈS ANNUEL



GCIG
GYNECOLOGIC
CANCER INTERGROUP

Canadian Cancer
Trials Group



Groupe canadien
des essais sur le cancer

An international randomized phase III trial comparing radical hysterectomy and pelvic node dissection vs simple hysterectomy and pelvic node dissection in patients with low-risk early-stage cervical cancer

A Gynecologic Cancer Intergroup study led by the Canadian Cancer Trials Group

CCTG CX.5 - SHAPE

NCT01658930

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On behalf of the SHAPE investigators



Objectifs

- **Décrire le concept de base de l'étude SHAPE.**
- **Nommer les critères d'inclusion et d'exclusion de l'étude SHAPE.**
- **Intégrer une stratégie d'évaluation rigoureuse dans la sélection des patientes pour une chirurgie moins radicale.**

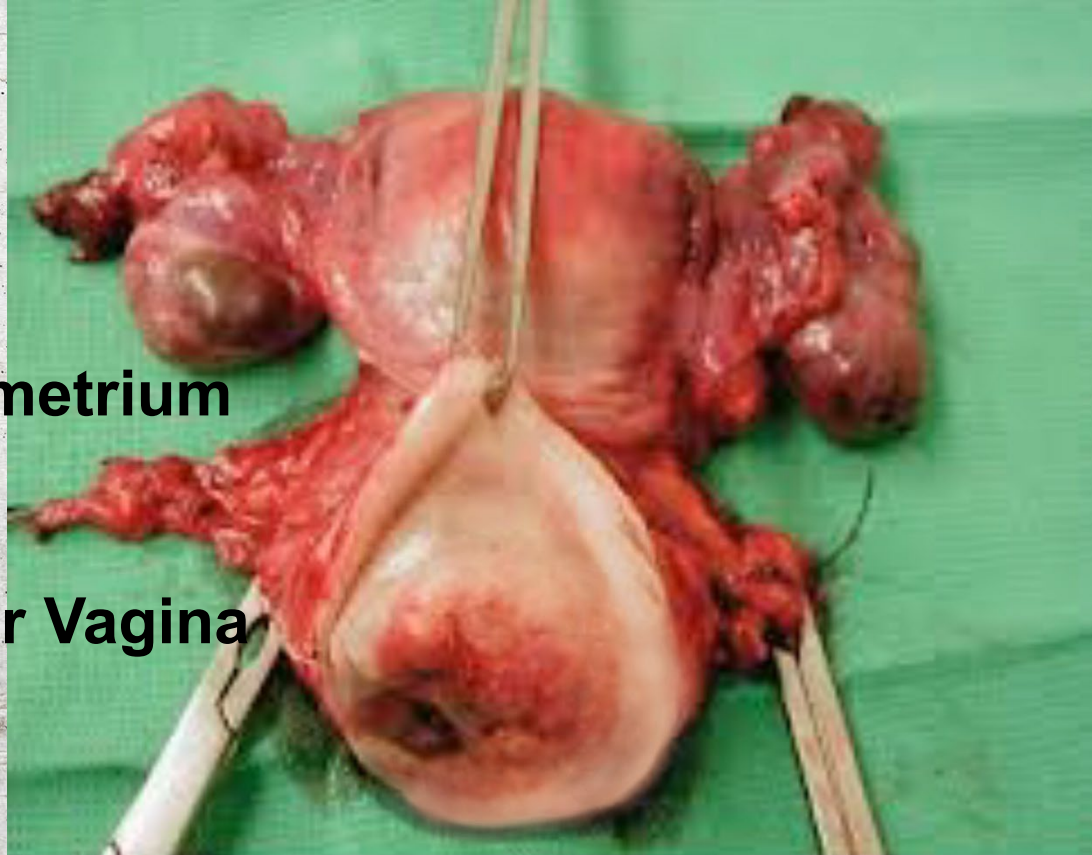
Conflit d'intérêt

- **Aucun conflit d'intérêt à déclarer en lien avec cette présentation**

SHAPE – Background and Rationale

- Cancer of the cervix is the second leading cause of cancer death in women worldwide
- As a result of effective screening in developed countries, the overall incidence of cervical cancer has decreased over the past 20 years, with a **higher proportion** of women presenting at a **younger age** and with **low-risk, early-stage disease**
- Although radical surgery is highly effective for the treatment of low-risk disease, women are at risk of suffering “**survivorship**” issues related to long-term **surgical side effects** including compromised bladder, bowel and sexual function

Types of Hysterectomy



Parametrium

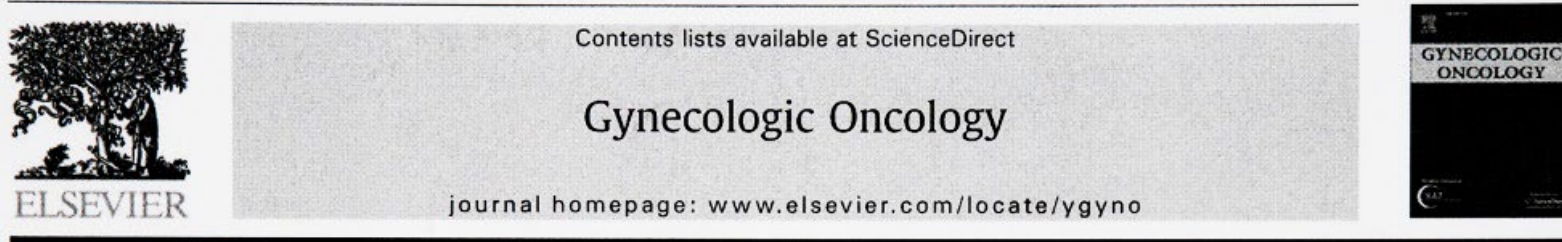
Upper Vagina

Radical Hysterectomy



Simple Hysterectomy

Less radical surgery



Review

Conservative management of early stage cervical cancer: Is there a role for less radical surgery?

Kathleen M. Schmeler*, Michael Frumovitz, Pedro T. Ramirez

Department of Gynecologic Oncology, The University of Texas M.D. Anderson Cancer Center, 1155 Herman Pressler Drive, Houston, TX 77030, USA

| Author | Year | Low-risk criteria | N | Parametrial involvement in low-risk group (%) |
|----------------|------|---|-----|---|
| Kinney [13] | 1995 | Squamous histology only, tumor <2 cm, no LVSI* | 83 | 0.0% |
| Covens [14] | 2002 | All histologies, tumor <2 cm, DOI** <10 mm, negative pelvic lymph nodes | 536 | 0.6% |
| Stegeman [15] | 2007 | Squamous, adenocarcinoma, adenosquamous or clear cell histology, tumor <2 cm, DOI** <10 mm, no LVSI*, negative pelvic lymph nodes | 103 | 0.0% |
| Wright [16] | 2008 | All histologies, tumor <2 cm, no LVSI*, negative pelvic lymph nodes | 270 | 0.4% |
| Frumovitz [19] | 2009 | Squamous, adenocarcinoma or adenosquamous histology, tumor <2 cm, no LVSI* | 125 | 0.0% |

*LVSI: lymphovascular space involvement

**DOI: depth of invasion

All retrospective data

N=1117 < 1%

Schmeler K et al. Gynecol Oncol 120:321, 2011

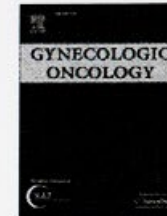
Less radical surgery



Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno



suggesting that less radical surgery
may be a safe option
associated with decreased morbidity
surgical de-escalation

| Author | Year | Study Characteristics | N | Endometrial involvement in low-risk group (%) |
|----------------|------|---|-----|---|
| Kinney [13] | 1995 | Squamous histology only, tumor <2 cm, no LVSI* | 83 | 0.0% |
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*LVSI: lymphovascular space involvement

**DOI: depth of invasion

All retrospective data

N=1117 < 1%

Hypothesis of the SHAPE trial (2012)

Less radical surgery – **simple hysterectomy** – will be associated with **similar efficacy** and **less surgical morbidity** compared to radical hysterectomy in patients with **low-risk disease**

Trial Schema

Low-risk cervical cancer as defined by:

- Squamous cell, adenocarcinoma, adenosquamous carcinoma
- Stage IA2 and IB1
- < 10 mm stromal invasion on LEEP/cone
- < 50% stromal invasion on MRI
- Max dimension of ≤ 20 mm
- Grade 1-3 or not assessable

Stratification:

1. **Cooperative Group**
2. **Sentinel node mapping (Yes vs No)**
3. **Stage (IA2 vs IB1)**
4. **Histological type (Squamous vs adenocarcinoma/adenosquamous)**
5. **Grade (1-2 vs 3 vs not assessable)**

R
A
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1

**Arm 1
(Control)
Radical
Hysterectomy***

**Arm 2
(Experimental)
Simple
Hysterectomy***

**Pelvic
recurrence
rate at 3 years**

*Regardless of treatment assignment, surgery will include **pelvic lymph node dissection** with optional sentinel lymph node (SN) mapping. If SN mapping is to be done, the mode is optional, but the laparoscopic approach is preferred.

CX.5 Endpoints

Primary Endpoints

- **Pelvic recurrence rate at 3 years (PRR3)**

Secondary Endpoints

- Pelvic relapse free survival (PRFS)
- Extra pelvic relapse free survival (EPRFS)
- Relapse free survival (RFS)
- Overall Survival (OS)
- Rates of sentinel node detection, parametrial involvement, involved surgical margins, positive pelvic nodes
- Patient reported outcomes

CX.5 Statistical Considerations

- **Non-inferiority (NI) Phase 3 design**
 - **Intention to Treat (ITT)** analysis as primary analysis
 - **Per-protocol (PP)** analysis, as secondary analysis
- Primary endpoint in original design
 - **Pelvic relapse free survival (PRFS)**
 - **49** pelvic relapses required for final analysis
- Primary endpoint **changed** to:
 - **Pelvic recurrence rate at 3 years (PRR3)** due to very low event rate
 - Amendment approved by CCTG Data and Safety Monitoring Committee (DSMC), June 2022

CX.5 Statistical Considerations

- PRR3 was estimated using **Kaplan-Meier** method
- NI of SH to RH is claimed when the upper 1-sided 95% confidence limit for the difference in PRR3 for SH to RH is lower than or equal to **4%**
- With **700** patients randomized and followed for a **minimum of 3 years**, the study has **85% power** to claim NI of SH to RH when PRR3 in both arms are assumed to be same

700 randomized between December 2012 and November 2019

12 countries
130 centers

350 to **simple**
hysterectomy and in
intention to treat (ITT)
population

350 to **radical**
hysterectomy and in
intention to treat (ITT)
population

7 never received
surgery

7 received radical
hysterectomy

2 received simple
hysterectomy

11 never received
surgery

338 in treated
population

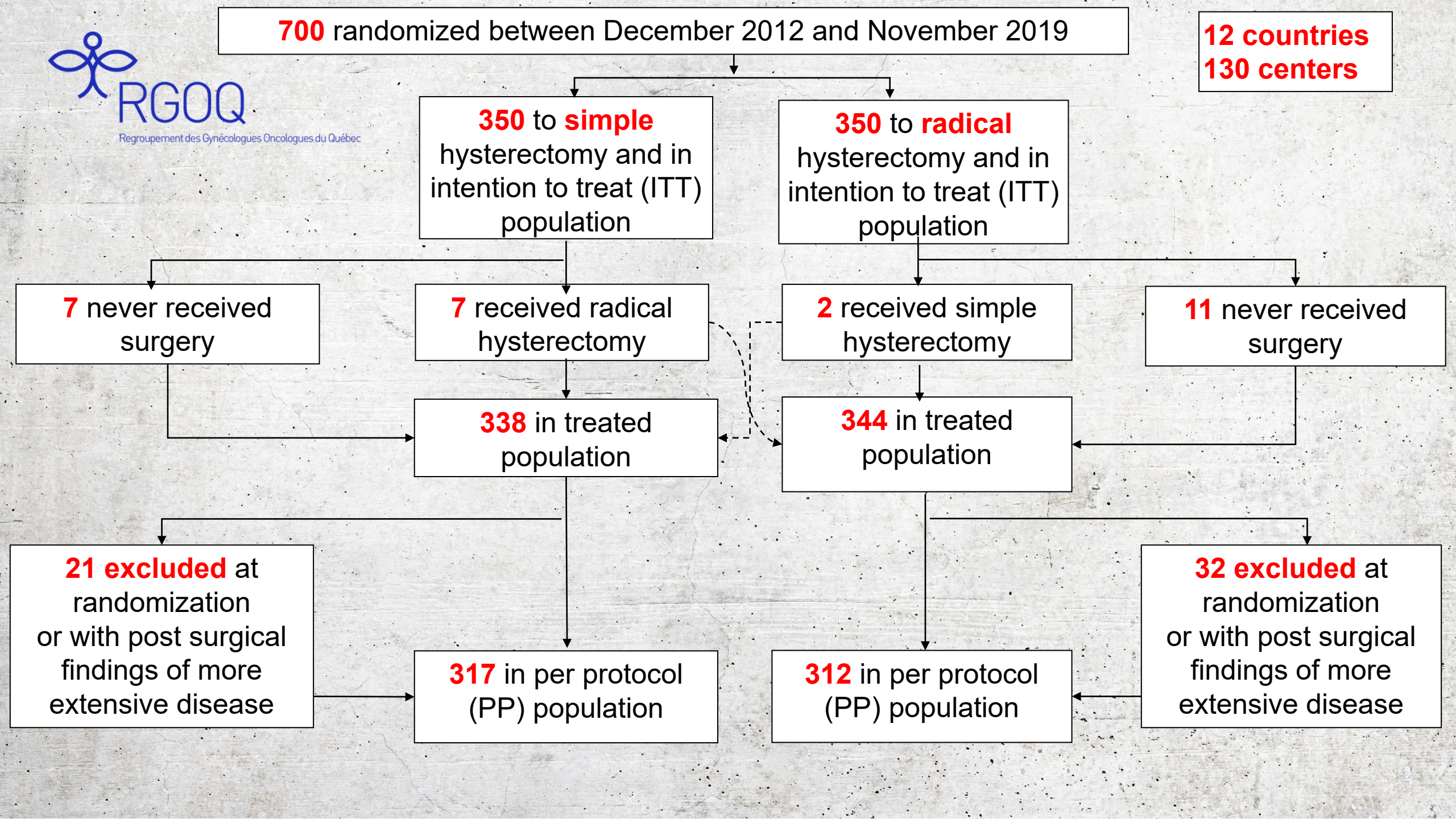
344 in treated
population

21 excluded at
randomization
or with post surgical
findings of more
extensive disease

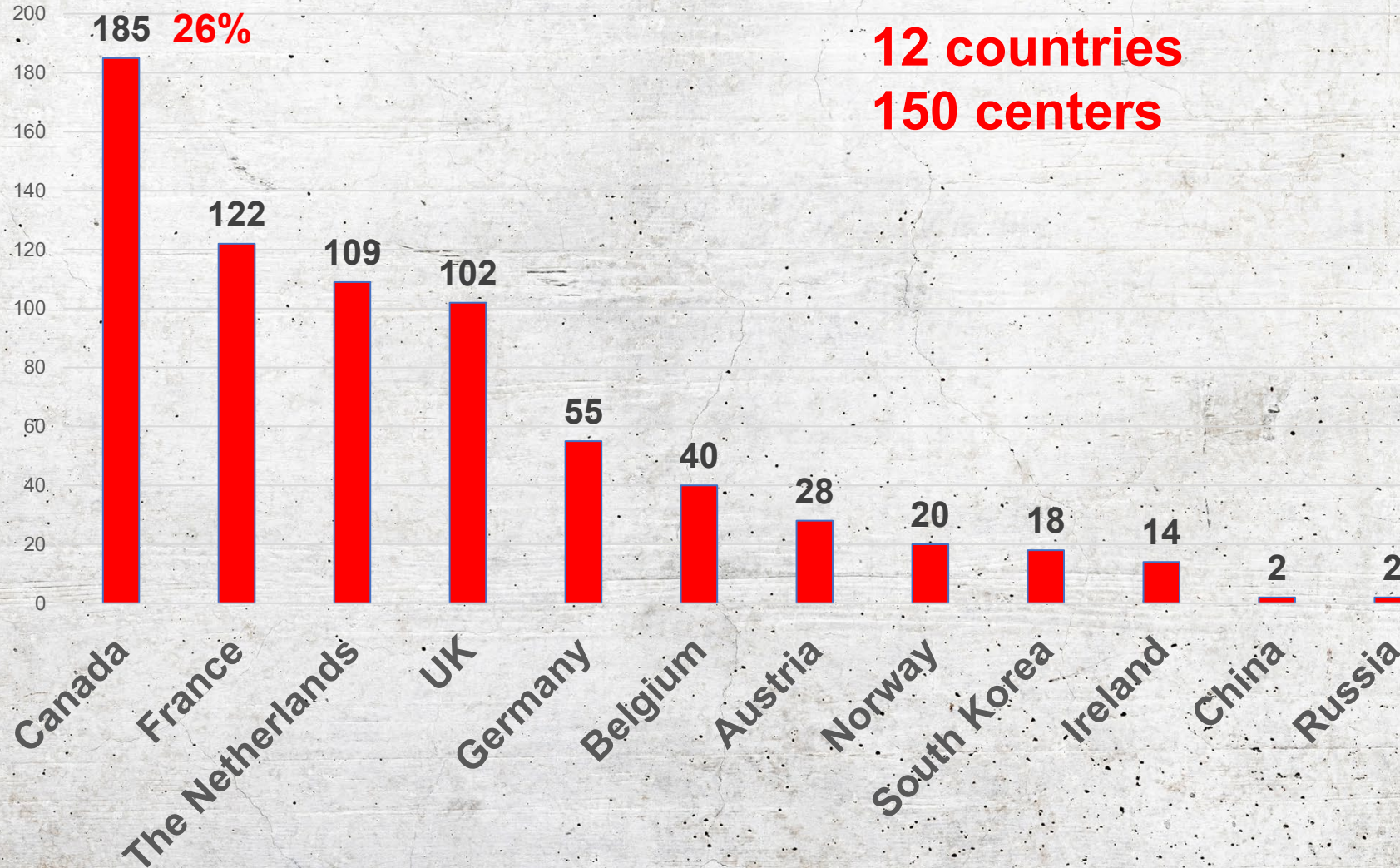
317 in per protocol
(PP) population

312 in per protocol
(PP) population

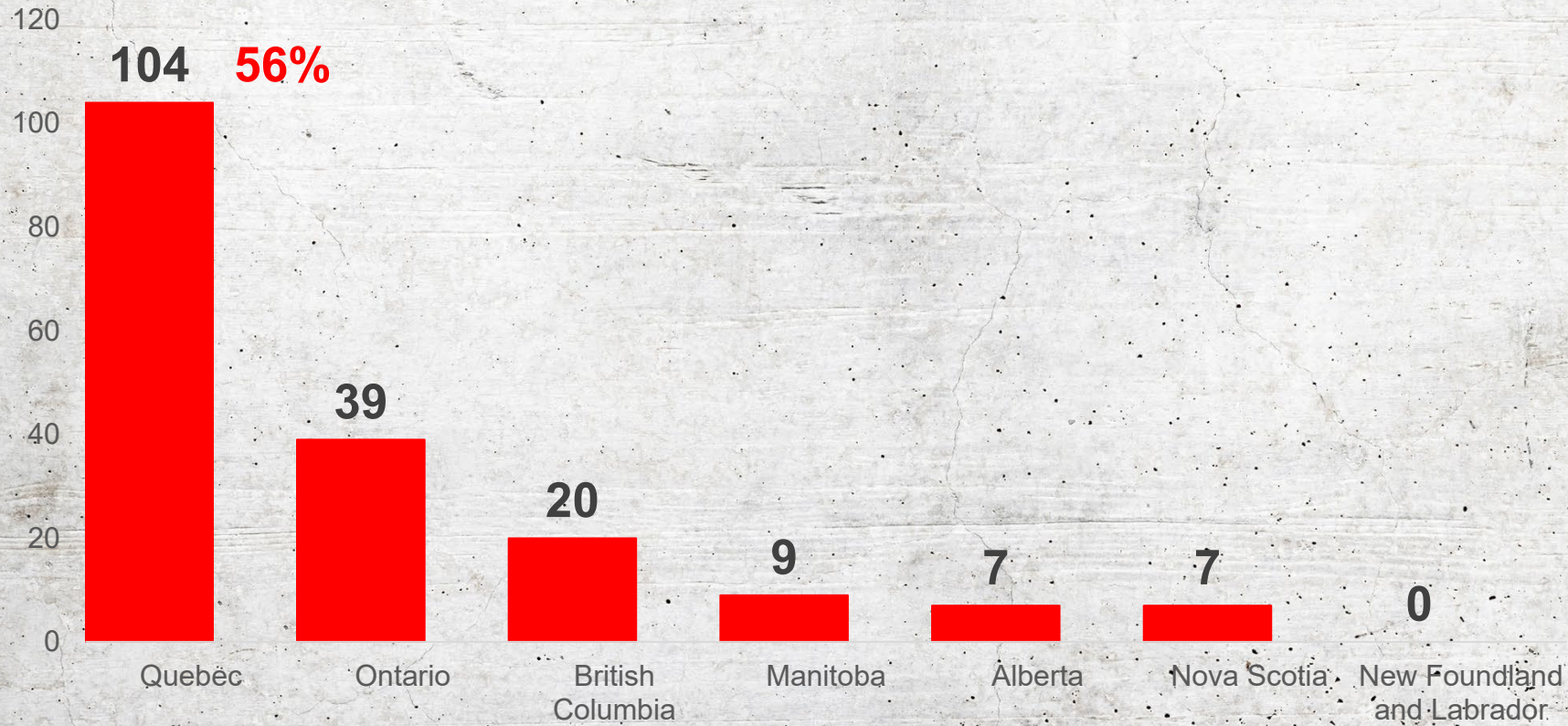
32 excluded at
randomization
or with post surgical
findings of more
extensive disease



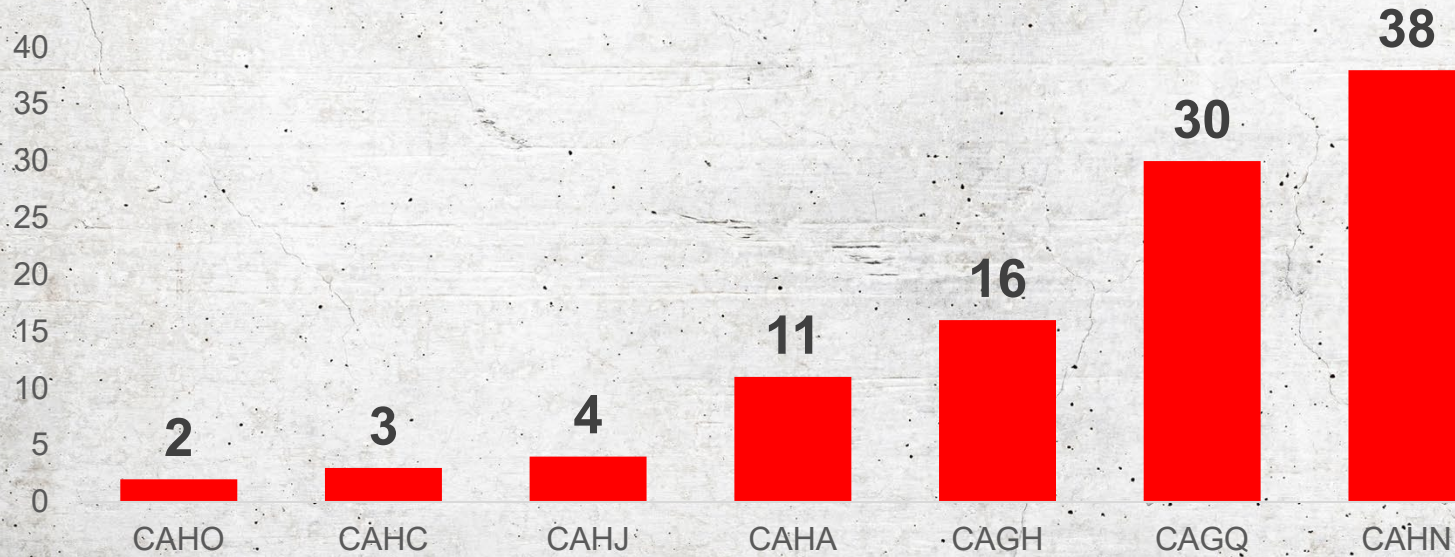
Accrual by Country



Accrual by Province- Canada



Accrual by Center -Quebec



Samouelian, Vanessa

Plante, Marie

Bessette, Paul

CAHN 25

CAGQ 17

CAGH 13

Key Baseline Patient Characteristics

| Characteristics | Simple Hysterectomy N=350 (%) | Radical Hysterectomy N=350 (%) | Total N=700 |
|------------------------------------|----------------------------------|-----------------------------------|------------------|
| Age (years): Median (range) | 42 (26-77) | 45 (24-80) | 44 (24-80) |
| • ≤ 50 years old (%) | 271 (77.4) | 246 (70.3) | 517 (73.9) |
| ECOG status: 0 | 336 (96) | 335 (95.7) | 671 (95.9) |
| BMI: median (range) | 25 (16.4-53.3) | 24.8 (16.1-52) | 24.8 (16.1-57.6) |
| Diagnostic Procedure | | | |
| • LEEP / Cone +/- Biopsy | 294 (84.0) | 267 (76.3) | 561 (80.1) |
| • Cervical Biopsy | 52 (14.9) | 77 (22.0) | 129 (18.4) |
| • Missing | 4 (1.1) | 6 (1.7) | 10 (1.4) |

Key Baseline Patient Characteristics

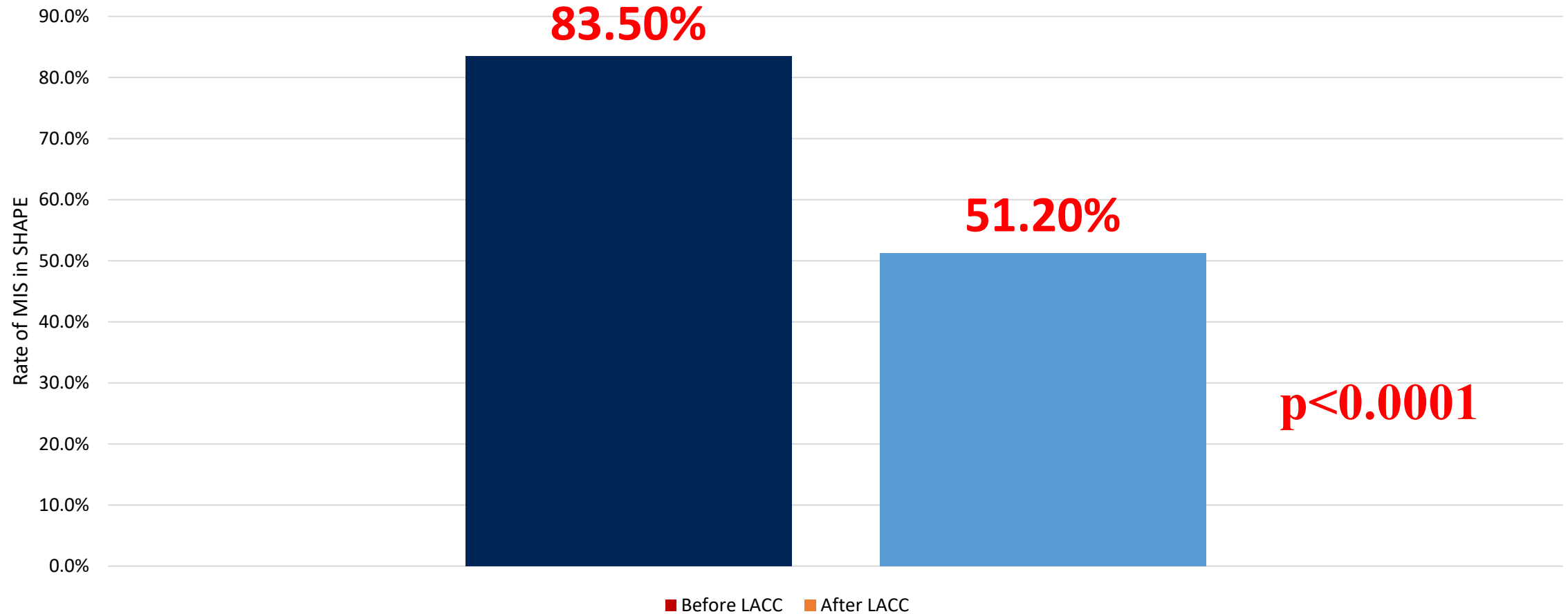
| Characteristics | Simple Hysterectomy N=350 (%) | Radical Hysterectomy N=350 (%) | Total N=700 |
|--------------------|----------------------------------|-----------------------------------|----------------|
| FIGO Stage: | | | |
| • IA2 | 30 (8.6) | 28 (8.0) | 58 (8.3) |
| • IB1 | 320 (91.4) | 322 (92.0) | 642 (91.7) |
| Histology | | | |
| • Squamous | 218 (62.3) | 214 (61.1) | 432 (61.7) |
| • Adenocarcinoma | 114 (32.6) | 131 (37.4) | 245 (35.0) |
| • Adenosquamous | 18 (5.1) | 5 (1.4) | 23 (3.3) |
| Grade: | | | |
| • 1 or 2 | 205 (58.6) | 210 (60.0) | 415 (58.2) |
| • 3 | 49 (14) | 49 (14) | 98 (14) |
| • Not assessed | 96 (27.4) | 91 (26) | 187 (26.7) |

All Treated Patients Post Surgery

| Characteristics | Simple Hysterectomy N=338 (%) | Radical Hysterectomy N=344 (%) | P-value |
|------------------------------------|----------------------------------|-----------------------------------|---------------|
| Type of Surgical Approach * | | | |
| • Abdominal | 57 (16.9) | 99 (28.8) | 0.0003 |
| • Laparoscopic | 188 (55.6) | 152 (44.2) | 0.0036 |
| • Robotic | 82 (24.3) | 87 (25.3) | 0.79 |
| • Vaginal | 11 (3.3) | 4 (1.2) | 0.07 |
| Sentinel Node Mapping | | | |
| • Planned | 126 (37.3) | 131 (38.2) | 0.87 |
| • Successful | 78/126 (61.9) | 83/131 (63.4) | 0.90 |

* Surgical approach: at the discretion of the surgeon; not a randomization factor

MIS in Relation to LACC trial publication



LACC was published November 15th 2018
SHAPE closed accrual November 29th 2019

All Treated Patients Post Surgery

| Key post surgical findings on final pathology | Simple hysterectomy N=338 (%) | Radical hysterectomy N=344 (%) | P-value |
|--|----------------------------------|-----------------------------------|---------|
| • Residual cervical cancer detected | 154 (45.6) | 163 (47.4) | 0.65 |
| • Lymphovascular space invasion (LVSI) | 45 (13.3) | 45 (13.1) | 1.00 |
| • Positive nodes (from sentinel or non sentinel nodes) | 11 (3.3) | 15 (4.4) | 0.55 |
| • Positive vaginal margins | 7 (2.1) | 10 (2.9) | 0.62 |
| • Positive parametrium | 0 | 6 (1.7)* | 0.03 |
| • Lesions > 2cm | 15 (4.4) | 14 (4.1) | 0.85 |

* 4/6 patients with positive parametrium had lesions > 2cm on final pathology.

Positive margins

| Positive margins | Simple Hysterectomy N=7 | Radical Hysterectomy N=10 | Total N=17 |
|------------------|----------------------------|------------------------------|---------------|
| MIS* | 5 (71.4) | 9 (90) | 14 (82) |
| Open | 2 (28.6) | 1 (10) | 3 (18) |

* MIS: laparoscopy and robotic surgery

All Treated Patients Post Surgery

| Adjuvant Treatment | Simple hysterectomy N=338 (%) | Radical hysterectomy N=344 (%) | P-value |
|--|----------------------------------|-----------------------------------|---------|
| • Adjuvant Post Operative Treatment | 31 (9.2) | 29 (8.4) | 0.79 |
| • Chemotherapy only | 1 | 0 | |
| • Radiation therapy only | 15 | 11 | |
| • Chemoradiation | 15 | 18 | |

Recurrences

| Events | Simple Hysterectomy N=350 (%) | Radical Hysterectomy N=350 (%) | Total N=700 (%) |
|--|----------------------------------|-----------------------------------|--------------------|
| Pelvic recurrences | 11 (3.1) | 10 (2.9) | 21 (3.0) |
| • Vaginal Vault | 9 (0.4) | 8 (2.3) | 17 (2.4) |
| • Parametrium | 1 (0.3) | 0 | 1 (0.1) |
| • Pelvic Lymph Nodes | 0 | 0 | 0 |
| • Other | 1 (0.3) | 2 (0.6) | 3 (0.4) |
| Extra Pelvic recurrences | 7 (2.0) | 2 (0.6) | 9 (1.3) |
| • Abdomen | 2 (0.6) | 0 | 2 (0.3) |
| • Para-aortic lymph nodes | 2 (0.6) | 2 (0.6) | 4 (0.6) |
| • Supraclavicular L N | 1 (0.3) | 0 | 1 (0.1) |
| • Other | 2 (0.6) | 0 | 2 (0.3) |
| Pelvic and extra pelvic recurrences | 3 (0.9) | 2 (0.6) | 5 (0.7) |
| Extra pelvic only recurrences | 4 (1.1) | 0 | 4 (0.6) |
| Pelvic or extra pelvic recurrences | 15 (4.3) | 10 (2.9) | 25 (3.6) |

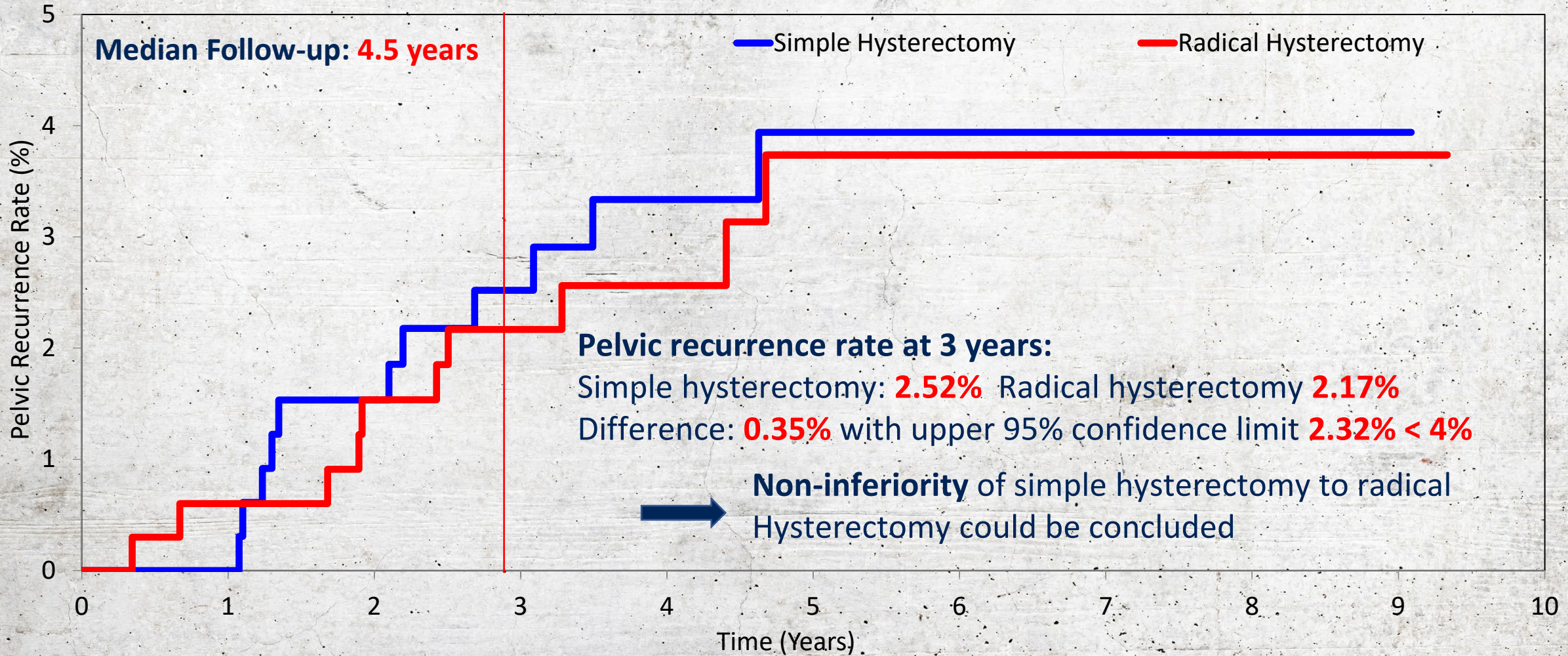
| | Number of Subjects (%) | | | |
|---|--------------------------------|-------------------------------|--------------------------------|-------------------------------|
| | Randomized | | Per protocol Analysis | |
| | Simple Hysterectomy N = 350 | Radical Hysterectomy N=350 | Simple Hysterectomy N = 317 | Radical Hysterectomy N=312 |
| Recurrence [§] | 15 (4.3) | 10 (2.9) | 12 (3.8) | 10 (3.2) |
| Pelvic recurrence | 11 (4.1) | 10 (2.9) | 10 (3.2) | 10 (2.9) |
| Vaginal Vault | 9 | 8 | 9 | 8 |
| Parametrium | 1 | 0 | 1 | 0 |
| Lower para-aortic and common iliac lymph node | 1 | 0 | 0 | 0 |
| Centro pelvic | 0 | 1 | 0 | 1 |
| Pelvic sidewall | 0 | 1 | 0 | 1 |
| Extra-pelvic recurrence | 7 (2.0) | 2 (0.6) | 4 (1.3) | 2 (0.6) |
| Abdomen | 2 | 0 | 0 | 0 |
| Para-aortic lymph nodes | 2 | 2 | 1 | 2 |
| Supraclavicular lymph nodes | 1 | 0 | 1 | 0 |
| Interaortocaval & obturator lymph nodes and vaginal vault | 1 | 0 | 1 | 0 |
| Vaginal introitus | 1 | 0 | 1 | 0 |
| Death | 7 (2.0) | 7 (2.0) | 3 (0.9) | 4 (1.3) |
| Cervical Cancer | 4 | 1 | 2 | 1 |
| Other primary malignancy | 1 | 3 | 0 | 2 |
| Other medical condition | 2 | 3 | 1 | 1 |

Deaths

| Events (ITT) | Simple Hysterectomy N=350 (%) | Radical Hysterectomy N=350 (%) | Total N=700 (%) |
|----------------------------|----------------------------------|-----------------------------------|--------------------|
| Deaths | 7 (2.0) | 7 (2.0) | 14 (2.0) |
| • Cervical Cancer | 4 (1.1) | 1 (0.3) | 5 (0.7) |
| • Other primary malignancy | 1 (0.3) | 3 (0.9) | 4 (0.6) |
| • Other medical condition | 2 (0.6) | 3 (0.9) | 5 (0.7) |

| Events (PP) | Simple Hysterectomy N=317 (%) | Radical Hysterectomy N=312 (%) | Total N=629 (%) |
|----------------------------|----------------------------------|-----------------------------------|--------------------|
| Deaths | 3 (0.9) | 4 (1.3) | 7 (1.1) |
| • Cervical Cancer | 2 (0.6) | 1 (0.3) | 3 (0.4) |
| • Other primary malignancy | 0 (0.0) | 2 (0.6) | 2 (0.3) |
| • Other medical condition | 1 (0.3) | 1 (0.3) | 2 (0.3) |

Pelvic Recurrence Rate (ITT)



| | | | | | | | | | | | |
|---------|-----|-----|-----|-----|-----|-----|----|----|----|---|---|
| Simple | 350 | 328 | 311 | 273 | 204 | 133 | 61 | 31 | 14 | 4 | 0 |
| Radical | 350 | 329 | 315 | 286 | 208 | 132 | 66 | 31 | 16 | 2 | 0 |

Subgroup**Difference in PRR3 and 90% CI****PRR3 (%)
on SH****PRR3 (%)
on RH****Difference (%)
(90% CI)**

Overall (ITT)

Stage

IA2

IB1

Histology

Squamous

Adenocarcinoma
/adenosquamous

Tumor grade

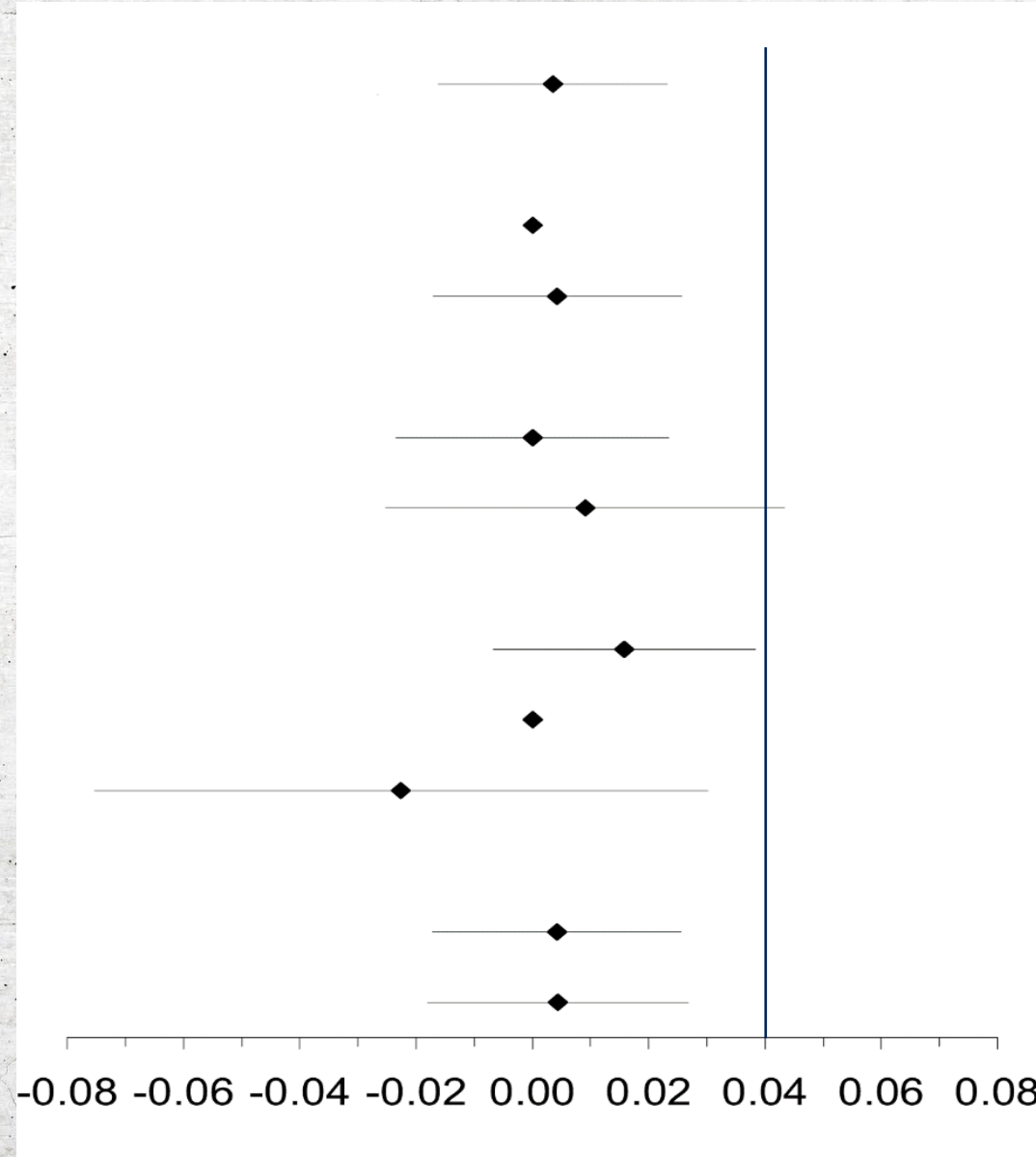
1-2

3

Not assessable

Per-protocol patients

Pre-defined

+Excluding eligibility
not met after surgery**SH is non-inferior to RH****SH is inferior to RH**



Regroupement des Gynécologues Oncologues du Québec

Secondary Efficacy Endpoints (ITT)

| Endpoints | Simple Hysterectomy N=350 | Radical Hysterectomy N=350 | | |
|---------------------------------------|------------------------------|-------------------------------|---|---------|
| | 3 year outcomes | | Hazard Ratio (90% confidence interval) | P-value |
| Pelvic Recurrence Free Survival | 97.5% | 97.8% | 1.12 (0.54-2.32) | 0.79 |
| Extra-Pelvic Recurrence Free Survival | 98.1% | 99.7% | 3.82 (0.79-18.4) | 0.10 |
| Relapse Free Survival | 96.3% | 97.8% | 1.54 (0.69-3.45) | 0.30 |
| Overall Survival | 99.1% | 99.4% | 1.09 (0.38-3.14) | 0.87 |

All Treated Patients Post Surgery

| Intraoperative complications | Simple Hysterectomy N=338 (%) | Radical Hysterectomy N=344 (%) | P-value |
|------------------------------|----------------------------------|-----------------------------------|---------|
| Intraoperative Injury | 24 (7.1) | 22 (6.4) | 0.77 |
| • Bladder | 3 | 9 | 0.14 |
| • Ureter | 3 | 5 | 0.73 |
| • Nerve | 5 | 2 | 0.28 |
| • Bowel | 2 | 2 | 1.00 |
| • Vein | 4 | 1 | 0.21 |
| • Other | 7 | 3 | 0.22 |

Surgery-Related Adverse Events

(All Grades with incidence $\geq 5\%$ in one of the Arms)

| Adverse Event | Simple Hysterectomy N=338 (%) | Radical Hysterectomy N=344 (%) | P value | Simple Hysterectomy N=338 (%) | Radical Hysterectomy N=344 (%) | P value |
|---------------------------------|--|-----------------------------------|-------------------|--|-----------------------------------|-------------------|
| | Within 4 weeks of surgery (<i>acute</i>) | | | After 4 weeks of surgery (<i>late</i>) | | |
| Any adverse event | 144 (42.6) | 174 (50.6) | 0.04 | 181 (53.6) | 208 (60.5) | 0.08 |
| • Abdominal pain | 33 (9.8) | 42 (12.2) | 0.33 | 36 (10.7) | 47 (13.7) | 0.24 |
| • Constipation | 16 (4.7) | 22 (6.4) | 0.40 | 13 (3.8) | 19 (5.5) | 0.37 |
| • Fatigue | 19 (5.6) | 23 (6.7) | 0.63 | 19 (5.6) | 28 (8.1) | 0.23 |
| • Paresthesia | 14 (4.1) | 22 (6.4) | 0.23 | 17 (5.0) | 22 (6.4) | 0.51 |
| • Peripheral sensory neuropathy | - (-) | - (-) | - (-) | 21 (6.2) | 13 (3.8) | 0.16 |
| • Urinary incontinence | 8 (2.4) | 19 (5.5) | 0.048 | 16 (4.7) | 38 (11.0) | 0.003 |
| • Urinary retention | 2 (0.6) | 38 (11.0) | <0.0001 | 2 (0.6) | 34 (9.9) | <0.0001 |
| • Dyspareunia | - (-) | - (-) | - (-) | 21 (6.2) | 19 (5.5) | 0.75 |
| • Pelvic pain | 19 (5.6) | 9 (2.6) | 0.054 | 23 (6.8) | 17 (4.9) | 0.33 |
| • Lymphedema | - (-) | - (-) | - (-) | 35 (10.4) | 36 (10.5) | 1.00 |
| • Hot flashes | - (-) | - (-) | - (-) | 14 (4.1) | 20 (5.8) | 0.38 |

Patient Reported Outcomes (PRO)

- Quality of Life and Sexual Health were assessed using validated questionnaires at different time points
 - EORTC QLQ-C30
 - EORTC QLQ-CX24
 - Female Sexual Function Index (FSFI)
 - Female Sexual Distress Scale (FSDS-R)
- Before randomization (baseline) and at 3, 6, 12, 24, and 36 months after surgery
 - Compliance (completion) rate **at baseline**
 - 73% for EORTC QOL assessments
 - 86% for sexual health assessments
 - Compliance (completion) rate **after baseline**
 - 56% to 69% for EORTC QOL assessments
 - 63% to 79% for sexual health assessments

Quality of Life and Sexual Health

| Scale | Effect Estimate* | P-value |
|--------------------------|------------------|---------|
| EORTC QLQ-C30 pain scale | -4.53 | p=0.02 |
| EORTC QLQ-CX24 | | |
| • Symptom experiences | -2.12 | p=0.02 |
| • Body Image | -5.22 | p=0.02 |
| • Sexual Worry | -6.67 | p=0.04 |
| • Sexual Activities | -7.59 | p=0.003 |
| • Sexual Enjoyment | -7.67 | p=0.049 |
| FSFI Desire | 0.37 | p=0.002 |
| FSFI Arousal | 0.38 | p=0.003 |
| FSFI Lubrication | 0.36 | p=0.008 |
| FSFI Total Score | 1.82 | p=0.006 |
| FSDS Total Score | -2.47 | p=0.02 |

Significant differences were seen between the 2 groups over time and **all were in favor of the simple hysterectomy group**

*From linear mixed models for change scores from baseline over time

Quality of Life and Sexual Health

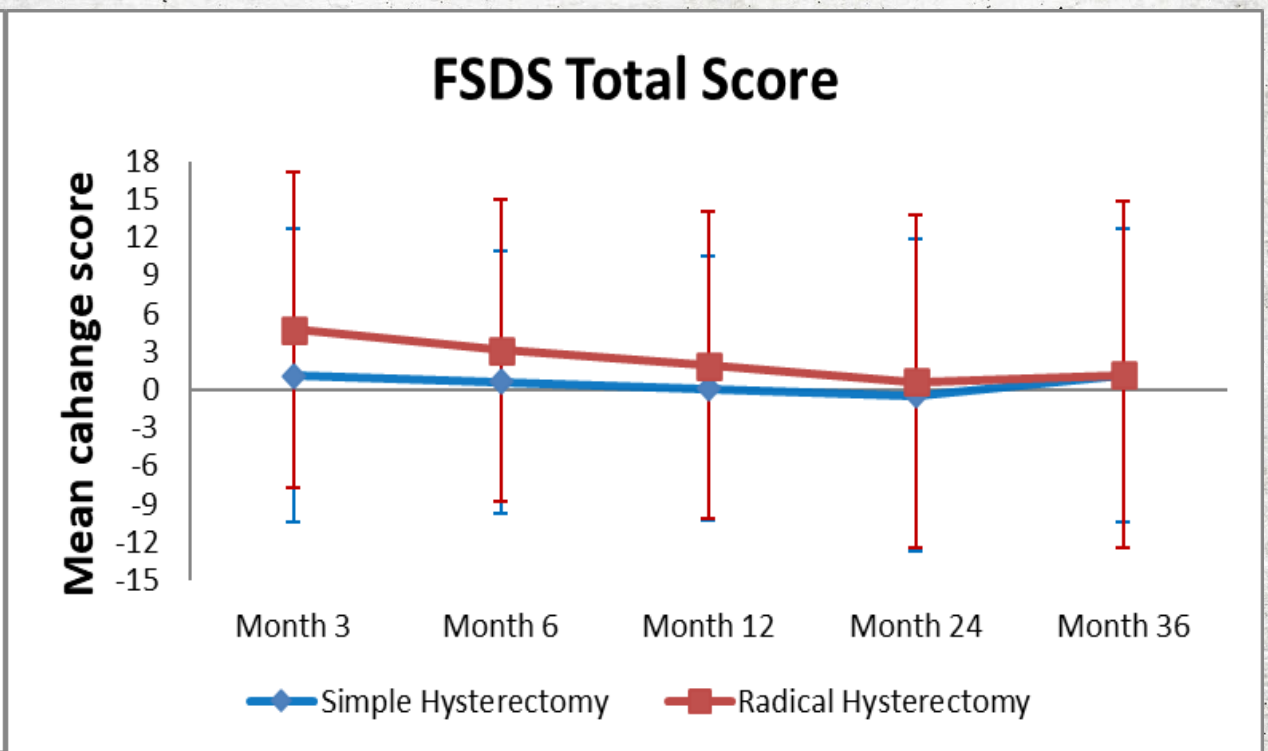
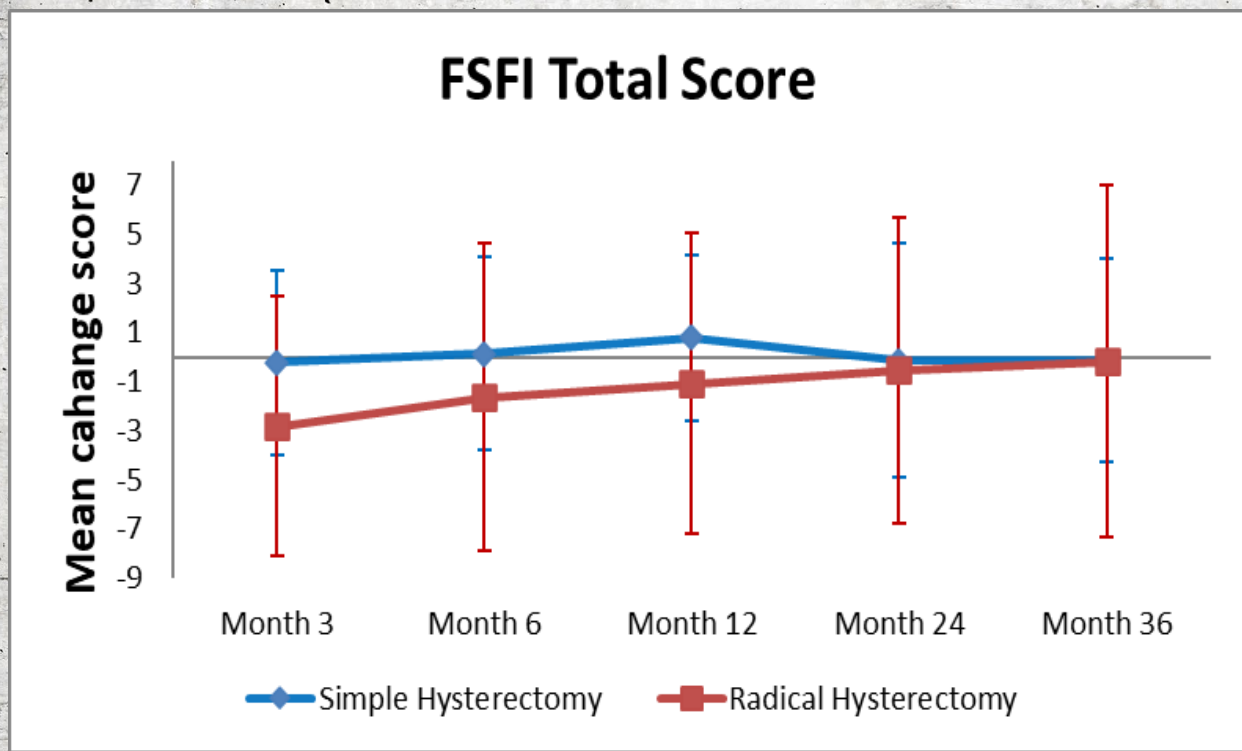
Sexual-Vaginal Functioning (EORTC QLQ-CX24): Lower Score is Better

| | SH (Mean change score) | RH (Mean change score) | P-value |
|-----------------|----------------------------------|----------------------------------|----------------|
| Month 3 | 4.41 | 16.03 | p<0.0001 |
| Month 6 | 0.93 | 11.85 | p<0.0001 |
| Month 12 | 0.94 | 9.16 | p<0.0001 |

Sexual Pain (FSFI Pain Scale): Higher Score is Better

| | SH (Mean change score) | RH (Mean change score) | P-value |
|-----------------|----------------------------------|----------------------------------|----------------|
| Month 3 | 0.03 | -0.78 | p=0.003 |
| Month 6 | 0.10 | -0.56 | p=0.02 |
| Month 12 | 0.35 | -0.22 | p=0.002 |

Quality of Life and Sexual Health



Higher score indicating a **better level of sexual function**

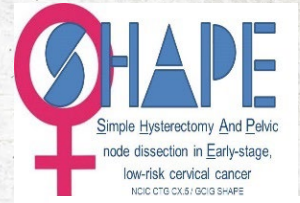
Higher score indicating a **greater level of sexual-related distress**

Conclusion

- In early-stage **low-risk** cervical cancer, pelvic recurrence rate at three years with **simple hysterectomy** was **not inferior** to radical hysterectomy
- Fewer urological surgical complications following **simple hysterectomy**
- Better quality of life and sexual health measures were seen following **simple hysterectomy**
- Following adequate / rigorous preoperative assessment, **simple hysterectomy** can now be considered the **new standard of care** for patients with low-risk early-stage cervical cancer, supporting the concept of **surgical de-escalation** in those patients
 - Stage IA2-IB1 **≤ 2cm**.
 - < 10 mm depth of stromal invasion (LEEP/cone) or
 - < 50% depth of stromal invasion (preop MRI)



Acknowledgements

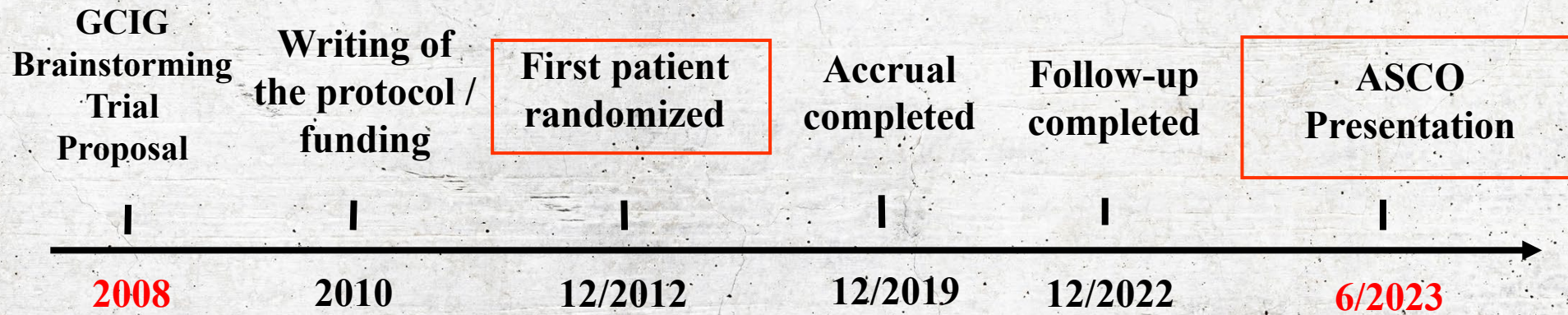


With thanks to the **700** hundred women who agreed to participate in this study and **all the investigators** and **clinical trial support staff** who ensured the success of the trial !



Funding to support this research was provided by:
- Canadian Cancer Society (grant #707213)
- Canadian Institutes of Health Research (grant #119446)

Story of SHAPE





Regroupement des Gynécologues Oncologues du Québec

Looooong way...

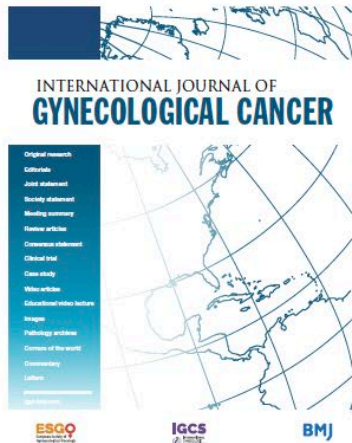


A venir





- Publications
 - NEJM: soumis 28 juillet...
 - QoL and Sexual Health
 - Health Economics
 - Relation entre récurrences et
 - Type d'hystérectomie (simple vs radicale)
 - L'approche chirurgicale (open vs MIS)
 - Maladie résiduelle sur la pièce d'hystérectomie (oui ou non)
 - Conisation/LEEP préop (oui ou non)
 - LVSI (oui ou non)
 - Sites de récurrence

SHAPE

- **Level-1 evidence**
- **Va probablement changer la pratique... et les guidelines !**



ConCerv: a prospective trial of conservative surgery for low-risk early-stage cervical cancer **N=100, phase II**

Kathleen M Schmeler ¹, Rene Pareja ², Aldo Lopez Blanco,³ Jose Humberto Fregnani,⁴ Andre Lopes,⁵ Myriam Perrotta,⁶ Audrey T Tsunoda,⁷ David F Cantú-de-León,⁸ Lois M Ramondetta,¹ Tarinee Manchana,⁹ David R Crotzer,¹⁰ Orla M McNally,¹¹ Martin Riege,¹² Giovanni Scambia,¹³ Juan Manuel Carvajal,¹⁴ Julian Di Guilmi,¹⁵ Gabriel J Rendon ¹⁶, Preetha Ramalingam,¹⁷ Bryan M Fellman,¹⁸ Robert L Coleman,¹⁹ Michael Frumovitz ¹, Pedro T Ramirez¹

HIGHLIGHTS

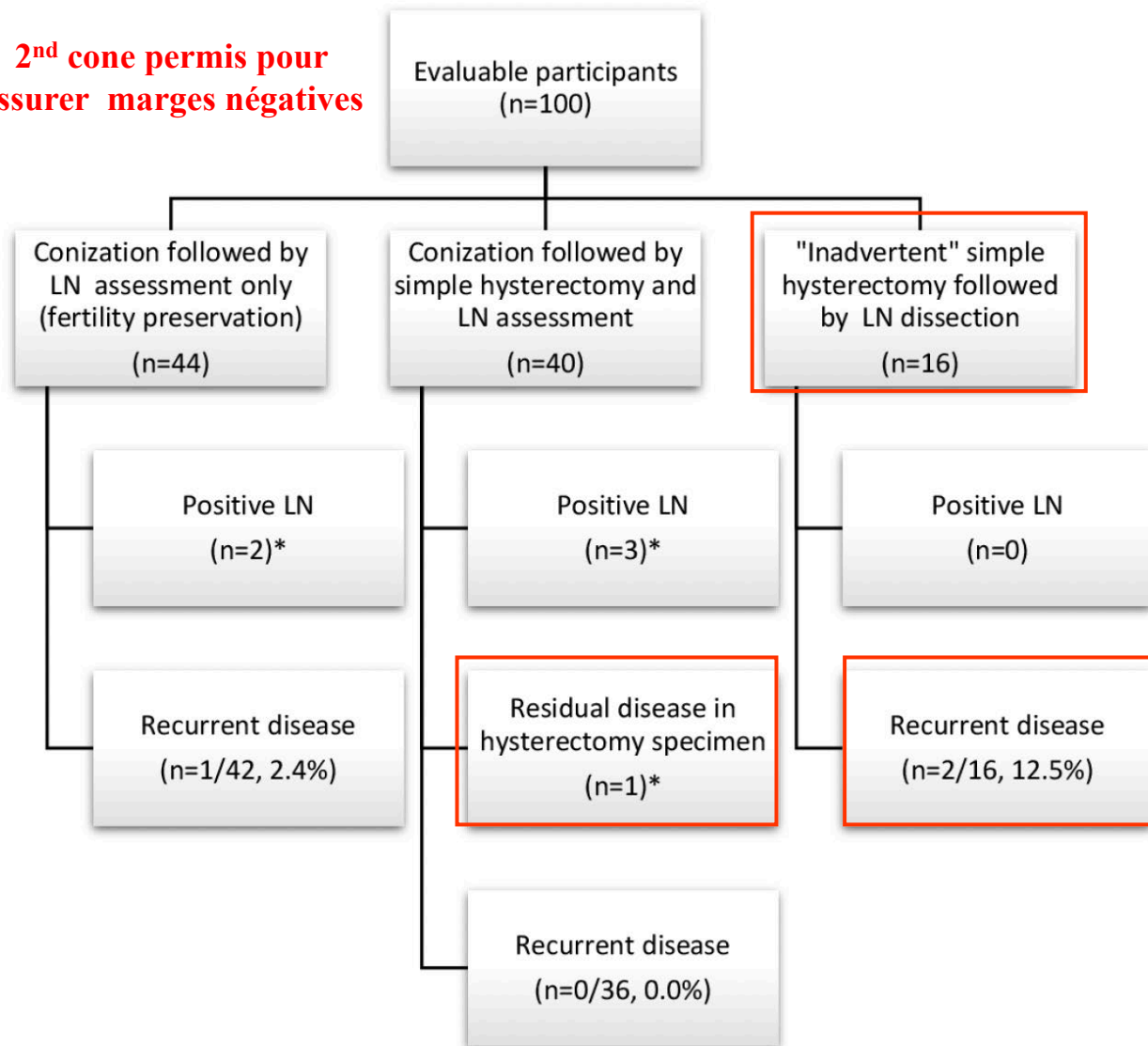
- Conservative surgery was associated with a **3.5% recurrence rate** in women with low-risk cervical cancer.
- The rate of **positive lymph nodes was 5%**, with lymph node assessment recommended in this low-risk population.
- Further study is needed to determine long-term outcomes and optimal pathologic criteria for conservative surgery.

CONCERV: critères de sélection

- **Cold knife conisation** pour déterminer l'**éligibilité**
- **Stade IA2-IB1; ≤ 2 cm** (examen clinique/imagerie)
- **Epidermoïde (all grades); Adéno (G1-2 seulement)**
- **LVSI négatif**
- **Pas d'évidence de maladie métastatique**
- **CT, IRM ou PET scan**
- **Profondeur d'infiltration ≤ 10 mm**
- **Marges de la conisation et ECC**
 - **Négatives** pour cancer (au moins 1 mm) ou lésion haut-grade

ConCerv Schema

2nd cone permis pour assurer marges négatives



**3.5% récidive
5% ggls positifs**



Stage **IA2–IB1** cervical carcinoma
(Based on **cone biopsy and all
conservative surgery criteria must be
met**):

- No LVSI
- Negative cone margins
- Squamous cell (any grade) or usual type adenocarcinoma (grade 1 or 2 only) **Excluded adenoca G3**
- Tumor size ≤ 2 cm
- Depth of invasion ≤ 10 mm
- Negative imaging for metastatic disease

→ **Extrafascial hysterectomy
+ pelvic lymphadenectomy⁹
(or SLN mapping)**

| | SHAPE | ConCerv |
|--------------------------|---------------------------|----------------------------|
| Type of study | Prospective Randomized | Prospective Single arm |
| | Phase 3 | Phase 2 |
| Number of patients | 700 | 100 |
| Stage | IA2/IB1 | IA2/IB1 |
| Size | ≤ 2cm | ≤ 2cm |
| Grade | All grades | Adenoca G3 excluded |
| LVSI | Allowed (13%) | Negative |
| Margins LEEP/Cone | Positive/negative | Negative |
| Residual disease | 46% | 2.5% |
| Positives nodes | 3.9% | 3.5% |
| Récidives | 3.0% | 3.5% |

Chirurgie moins radicale

Est-ce que l'hystérectomie simple
EST SECURITAIRE dans les
cancers du col utérin débutants ?

Oui... **mais...**

Attention

- **Rester à l'intérieur des paramètres de l'étude**
 - **Stage IA2-IB1 $\leq 2\text{cm}$**
 - **< 10 mm depth** de profondeur d'infiltration (LEEP/cone) or
 - **< 50% depth** de profondeur d'infiltration (preop MRI)
- **Evaluation préopératoire rigoureuse / méticuleuse**
 - **Qualité de la chirurgie**
- **Examen pathologique de bonne qualité**
 - **Taille de la lésion (LEEP/cone)**
 - **Le statut des marges**
 - **Profondeur d'infiltration du stroma cervical**
- **IRM de bonne qualité / bonne interprétation**
 - **Taille de maladie résiduelle**
 - **Profondeur d'infiltration du stroma cervical**

Statut des Marges

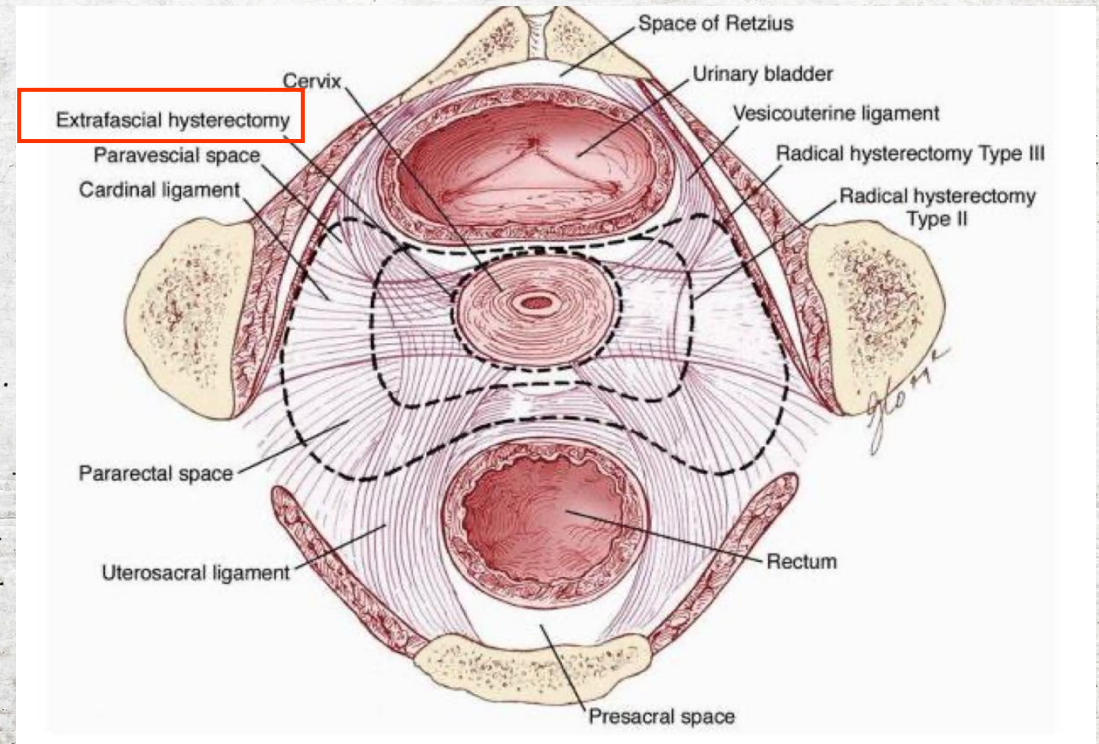
- Hystérectomie **extrafasciale**
- **SHAPE**: Demandait **5mm** vagin pour assurer des marges négatives...



Avec MIS

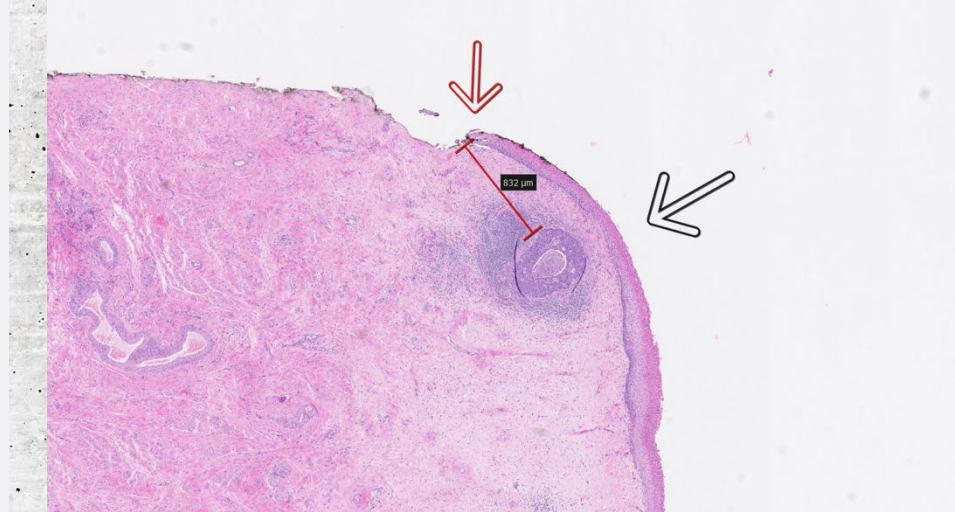
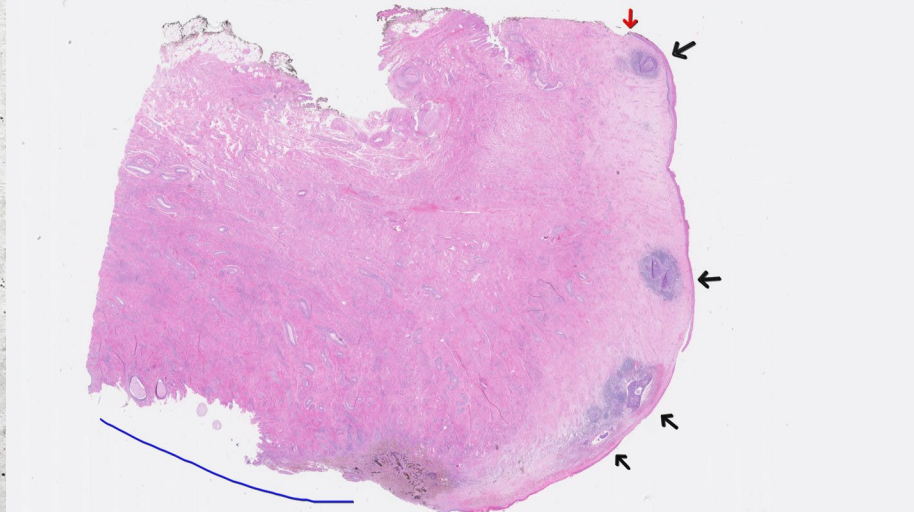
significant cautery artefacts

“beaten up” specimen; “chopped” edges



Type A – Querleu classification

Maladie microscopique post LEEP



LEEP/Conisation préopératoire

- Marges négatives **NE GARANTISSENT PAS** qu'il n'y aura pas de maladie résiduelle dans le spécimen d'hystérectomie, même si IRM/examen clinique normal
 - Ne peut donc pas garantir la "sécurité" de l'approche MIS
 - Toujours penser qu'il reste peut-être de la maladie
 - Donc... faire bien attention!

Post LEEP/cone évaluation

- **Examen clinique**
 - **Limites particulièrement pour les lésions endocervicales**
- **IRM post LEEP/cone**
 - **Particulièrement difficile à interpréter**
 - **Changements inflammatoires / modifications post cone**
 - **Très difficile de distinguer si changements post cone vs maladie résiduelle**
 - **IRM ne peut voir la maladie microscopique !**
 - **Risques de **sur** ou de **sous-estimer** la néoplasie résiduelle**
- **Dans SHAPE,**
 - **On a vu des discordances importantes entre IRM preop et le rapport de pathologie...**

Changements post cone à l'IRM

- **Conisation sous AG:**
- **Adenoca col G1**
- **Taille: 1.6 cm, Silva A (LVI-)**
- **Profondeur : 11 mm**
- **Marges négatives**
- **TEP négatif**

IRM post cone



IRM post cone

OPINION

Patiente qui aurait eu une conisation avec changements au col reliés à cela. Sous cette réserve, image compatible avec une néoplasie de regard la lèvre antérieure du col, qui nous paraît envahissante vers le fornix antérieur du vagin se manifestant par un épaississement du fornix et de la paroi antérieure au versant gauche du vagin, représentant une extension vaginale au tiers supérieur. Malgré qu'il n'y ait pas de franche masse paramétriale notée, on ne peut pas exclure un minime envahissement paramétrial à gauche.

FIGO IIb. Pas de franche extension vers le corps de l'utérus.

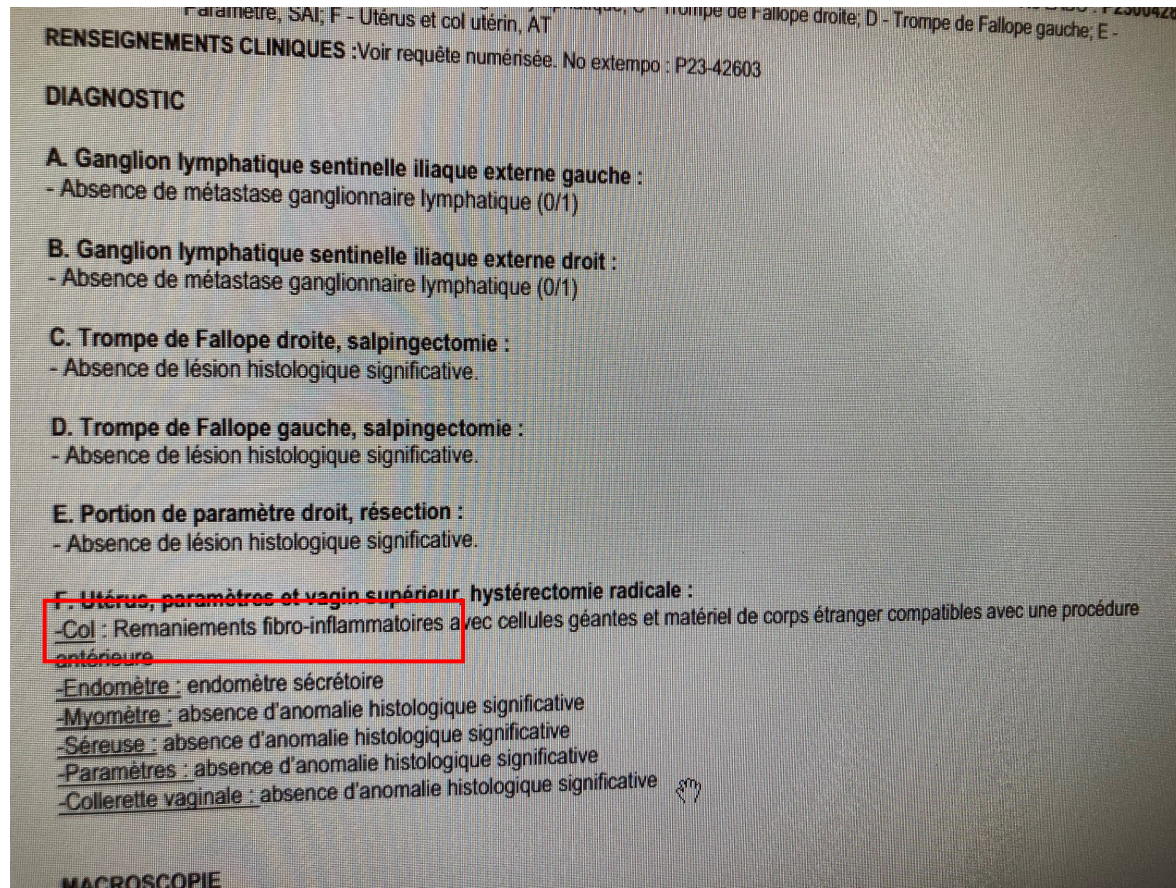
Pas d'anomalie visualisée en regard de la vessie. Pas d'adénomégalie décelée.

Opinion :

Chez cette patiente qui a eu une conisation en avril dernier, avec comme diagnostic un adénocarcinome du col de l'utérus, j'identifie à l'exocol un petit foyer nodulaire de signal intermédiaire T2 dont la nature exacte ne peut être déterminée sur cette étude. S'il s'agissait d'un résidu tumoral, celui-ci mesure maximale 13 mm et demeure confiné par le stroma cervical sans extension paramétriale. On observe un aspect un peu redondant et oedématisé de la paroi vaginale au niveau du fornix latéral gauche, qui est en signal intermédiaire T2, par contre il n'y a pas de restriction de la diffusion à ce niveau, il y a un rehaussement accru linéaire, je crois qu'il peut s'agir uniquement de changements inflammatoires post-procédure. Pas d'adénopathie.

Relecture

Patho finale



IRM post LEEP

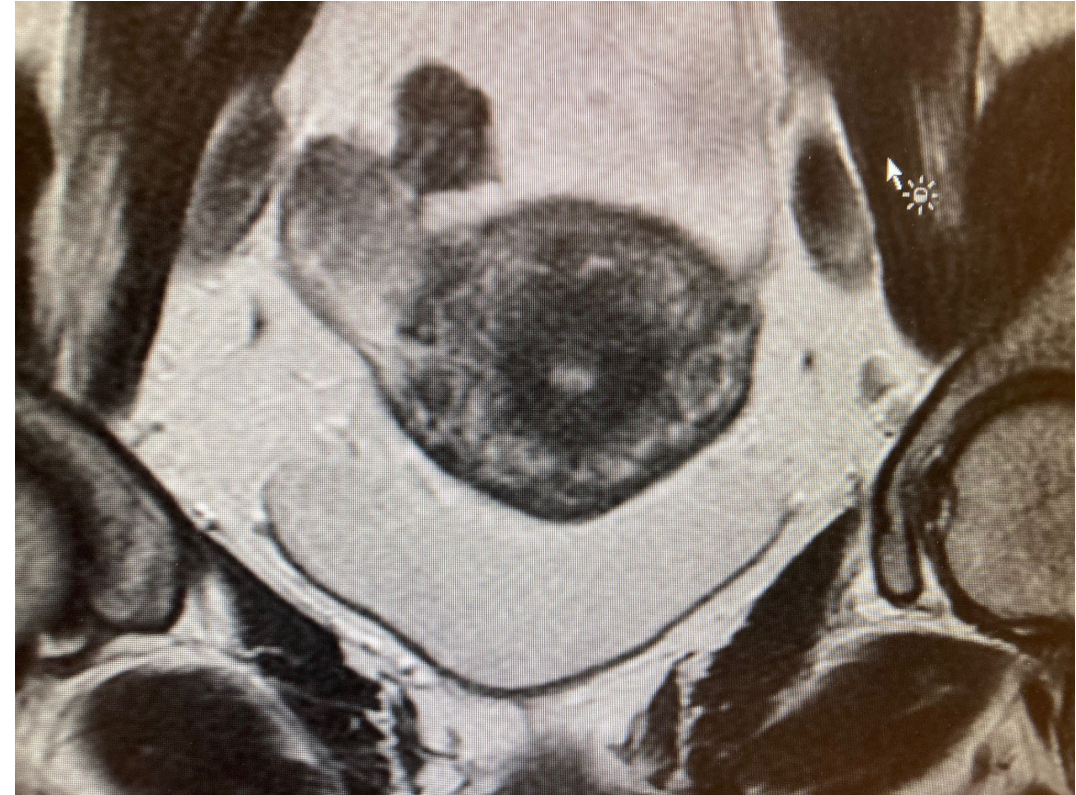
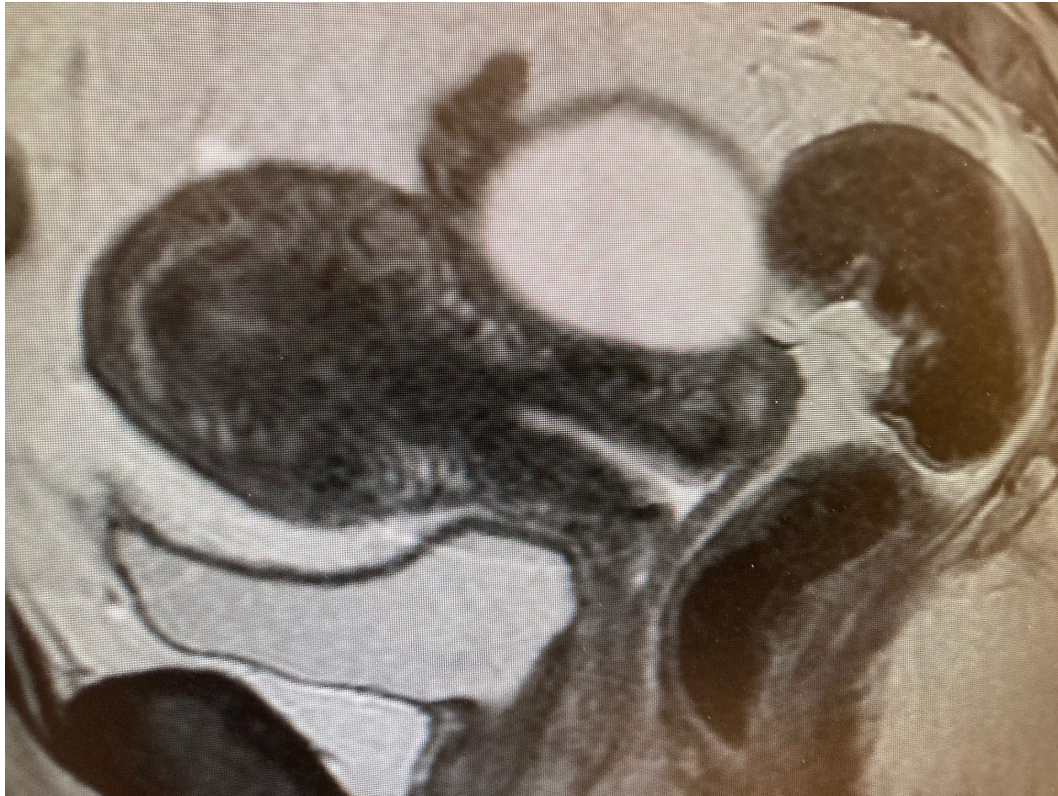
LEEP

- Adenoca G1
- Silva A, LVI-
- 3.3mm profondeur
- Marges négatives pour cancer (0.7mm)
- AIS/LIGE à la marge
- Reprise latérale négative
- CEC/BE négatif

Examen Clinique post LEEP

- normal
- pas de lésion visible

IMC 45



Opinion :

Patiente connue pour néoplasie du col de l'utérus. On observe au col des remaniements post-LEEP, mais il n'y a pas de lésion macroscopique résiduelle identifiable. Présence de petits fibromes utérins. Il y a des kystes ovariens bilatéraux uniloculaires simples. Pas de caractéristique complexe, mais le plus gros atteint tout de même 6 cm à droite. Pas d'adénopathie de calibre pathologique. Petit kyste arthrosynovial à départ de l'articulation interfaccettaire droite de L4-L5 se projetant au récessus droit.

Patho finale

- **Hystérectomie simple/GS**
 - Robot
 - Pas de manipulateur
- **Patho**
 - Adénocarcinome, G1, Silva A
 - Pas de lésion visible macroscopiquement.... Mais
 - Cancer microscopique présent sur 4 coupes
 - **Infiltration 4/9 mm (44%)**
 - Marges négatives/GS négatifs

Invisible cervical cancers on MRI: Can the type of histology (SCC versus non-SCC) influence surgical planning?

Jungeun Jeon¹, Byung Kwan Park^{2*}, Jeong-Won Lee^{1*}, Chel Hun Choi¹, Yoo-Young Lee¹, Tae-Joong Kim¹ and Byoungi-Gie Kim¹

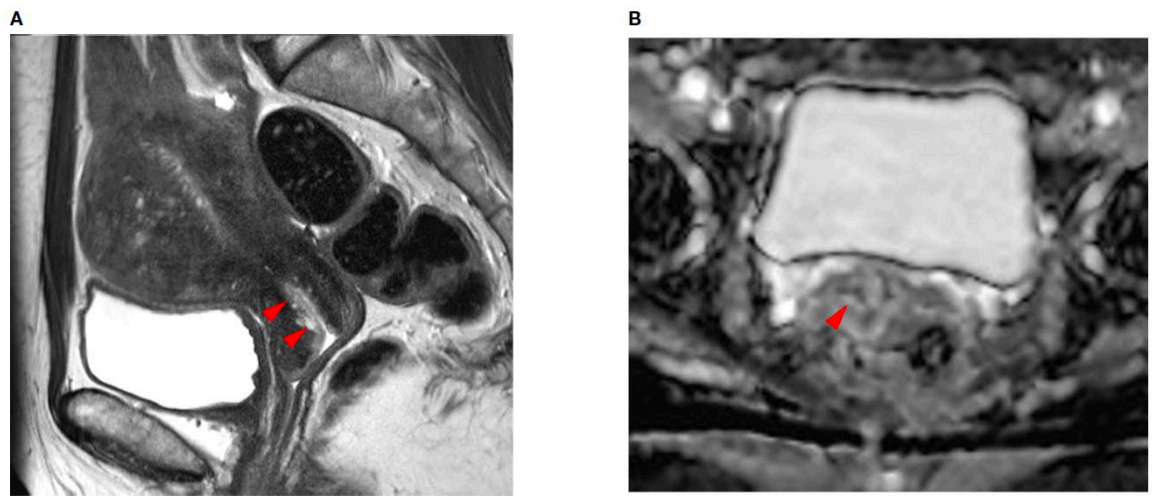


FIGURE 2
 A 48-year-old woman with endocervical adenocarcinoma. (A) The T2-weighted sagittal MR image shows no tumor in the uterine cervix. The red arrows indicate a poorly demarcated cystic mass, which was preoperatively interpreted as normal endocervical glands. (B) The apparent diffusion coefficient (ADC) axial image shows no focal lesion with low ADC values in the cervical canal (red arrowhead). However, the pathologic report confirmed that there was a residual tumor in the endocervical canal. The tumor size was measured as 2.0 × 1.5 cm and the depth of stromal invasion was 0.4 cm in a 1.3-cm cervical wall. It was well-correlated with the endocervical lesion in (A). Tumor invasion to the lymphovascular space, vagina, and parametrium and lymph node metastasis were all negative.

SCC cervical cancer tends to manifest as a solid tumor on MRI, and thus, the tumor size is easily measured

Tumor margin of non-SCC cervical cancer is not easily demarcated on preoperative MRI because a cystic component is frequent

CAS CLINIQUES

- **MISES EN SITUATIONS**

Chirurgie moins radicale

- **Patiente a eu LEEP qui montre un cancer épidermoïde de 1.5 cm avec une profondeur d'infiltration du stroma cervical de 12 mm**
- **Est-elle une candidate pour une hystérectomie simple ?**

Chirurgie moins radicale

- **Patiente a eu LEEP qui montre un cancer épidermoïde de 1.5 cm avec une profondeur d'infiltration du stroma cervical de 12 mm**
- **Est-elle une candidate pour une hystérectomie simple ?**
- **Selon ConCerv/SHAPE... non car profondeur d'infiltration >10mm**

Chirurgie moins radicale

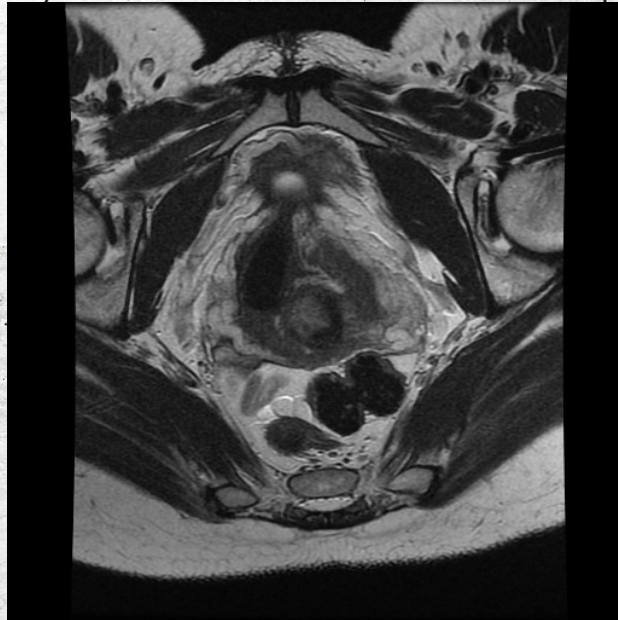
- **Patiente a un cone qui démontre un adénocarcinome de 1.8 cm avec marges endocervicales positives**
- **Est-elle une candidate pour une hystérectomie simple ?**

Chirurgie moins radicale

- **Patiente a un cone qui démontre un adénocarcinome de 1.8 cm avec marges endocervicales positives**
- **Est-elle une candidate pour une hystérectomie simple ?**
- **Selon ConCerv, elle doit avoir un 2ième cone**
 - Pour assurer des marges négatives
- **Selon ConCerv/SHAPE, elle devrait avoir une IRM préop**
 - Lésion résiduelle endocervicale (environ 7mm)
- **Donc... selon ConCerv/SHAPE... non car lésion >2cm**

Chirurgie moins radicale

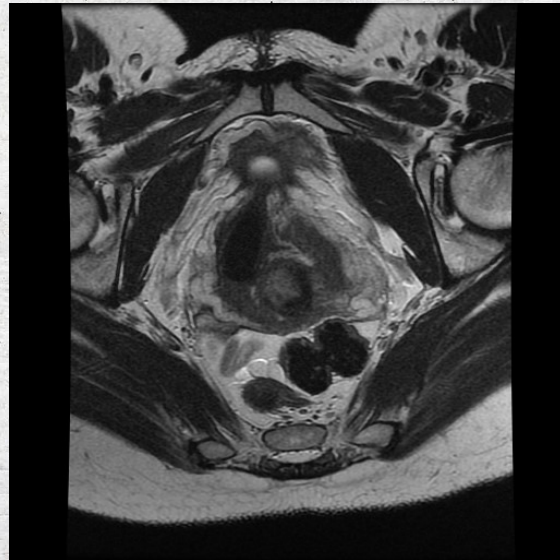
- **Patiente a une lésion visible au col < 2cm**
- **Biopsie confirme cancer épidermoïde**
- **Est-elle une candidate pour une hystérectomie simple ?**



IRM pelvien

Chirurgie moins radicale

- **Patiente a une lésion visible au col < 2cm**
- **Biopsie confirme cancer épidermoïde**
- **Est-elle une candidate pour une hystérectomie simple ?**
- **Selon SHAPE... non car profondeur infiltration > 50% à l'IRM**



Chirurgie moins radicale: **mes craintes...**

- **Gynécologues généraux (et même gyneco oncos!) concluent que le cancer du col peut maintenant être traité “jusse avec une simple” ...**
- **Sans une compréhension complète de la pathologie et imagerie**

Chirurgie moins radicale

- Importance de bien comprendre la **pathologie**
 - Taille de la lésion sur LEEP/cone
 - Etat des marges
 - Profondeur infiltration du stroma cervical
- Résultats de **IRM**
 - Taille de la lésion résiduelle
 - Profondeur infiltration stroma cervical

Chirurgie moins radicale

C'est OK d'être moins radical

C'est OK de faire chirurgie MIS

C'est OK de préserver fertilité

**Mais... pas au prix de mettre en péril la
survie des patientes...**

Chirurgie moins radicale

C'est OK d'être moi

C'

FAIRE PREUVE DE **JUGEMENT**

NE JAMAIS SOUS-ESTIMER LE CANCER DU COL

Mais... ne prenez pas le risque de mettre en péril la survie des patientes...

Outcomes by **Surgical Approach** and Treatment

| Endpoints | Abdominal | | MIS* | | Hazard Ratio** (95% CI) | P-value** |
|-------------------------------|---------------|-------------------|---------------|-------------------|----------------------------|-----------|
| | #Events /N | 3-year rate(%) | #Events /N | 3-year rate(%) | | |
| Pelvic recurrence | | | | | | |
| • Simple Hysterectomy | 2/57 | 3.89 | 9/281 | 2.31 | 1.26 (0.25-6.35) | 0.78 |
| • Radical Hysterectomy | 3/99 | 2.21 | 7/243 | 2.14 | 1.27 (0.31-5.24) | 0.74 |
| • All with treatment | 5/156 | 2.83 | 16/524 | 2.23 | 1.13 (0.39-3.22) | 0.83 |
| Extrapelvic recurrence | | | | | | |
| • Simple Hysterectomy | 1/57 | 1.85 | 6/281 | 1.94 | 0.76 (0.08-6.88) | 0.81 |
| • Radical Hysterectomy | 1/99 | 0.00 | 1/243 | 4.18 | 1.32 (0.08-21.2) | 0.84 |
| • All with treatment | 2/156 | 0.67 | 7/524 | 1.22 | 0.92 (0.18-4.82) | 0.92 |

*including laparoscopic, robotics, and vaginal approaches

**adjusted for treatment (for all with treatment only), age, race, intended use of sentinel node mapping, stage, histologic type, and histologic grade

Outcomes by **Surgical Approach** and Treatment

| Endpoints | Abdominal | | MIS* | | Hazard Ratio** (95% CI) | P-value** |
|----------------------------------|---------------|-------------------|---------------|-------------------|----------------------------|-----------|
| | #Events /N | 3-year rate(%) | #Events /N | 3-year rate(%) | | |
| Pelvic or extrapelvic recurrence | | | | | | |
| • Simple Hysterectomy | 3/57 | 5.67 | 12/281 | 3.47 | 1.38 (0.36-5.32) | 0.22 |
| • Radical Hysterectomy | 3/99 | 2.21 | 7/243 | 2.14 | 1.27 (0.31-5.24) | 0.74 |
| • All with treatment | 6/156 | 3.47 | 19/524 | 2.84 | 1.20 (0.46-3.15) | 0.13 |
| Death from any cause | | | | | | |
| • Simple Hysterectomy | 0/57 | 0.00 | 7/281 | 1.14 | 0.00 (0.00-) | 1.00 |
| • Radical Hysterectomy | 3/99 | 1.03 | 4/243 | 0.44 | 2.69 (0.56-12.9) | 0.22 |
| • All with treatment | 3/156 | 0.65 | 11/524 | 0.81 | 1.00 (0.27-3.71) | 1.00 |

*including laparoscopic, robotics, and vaginal approaches

**adjusted for treatment (for all with treatment only), age, race, intended use of sentinel node mapping, stage, histologic type, and histologic grade

Outcomes by **Diagnostic Procedure** and Treatment

| Endpoints | LEEP/Cone* | | Biopsy only | | Hazard Ratio** (95% CI) | P-value** |
|-------------------------------|---------------|-------------------|---------------|-------------------|----------------------------|-------------|
| | #Events /N | 3-year rate(%) | #Events /N | 3-year rate(%) | | |
| Pelvic recurrence | | | | | | |
| • Simple Hysterectomy | 7/294 | 1.82 | 4/52 | 6.85 | 0.25 (0.07-0.92) | 0.04 |
| • Radical Hysterectomy | 7/267 | 1.63 | 3/77 | 4.33 | 0.76 (0.18-3.25) | 0.71 |
| • All with treatment | 14/561 | 1.74 | 7/129 | 5.25 | 0.46 (0.18-1.17) | 0.10 |
| Extrapelvic recurrence | | | | | | |
| • Simple Hysterectomy | 6/294 | 1.85 | 1/52 | 2.13 | 1.17 (0.13-10.1) | 0.89 |
| • Radical Hysterectomy | 1/267 | 0.00 | 1/77 | 1.41 | 0.14 (0.01-2.28) | 0.16 |
| • All with treatment | 7/561 | 0.97 | 2/129 | 1.69 | 0.64 (0.13-3.21) | 0.59 |

*With or without cervical biopsy

**adjusted for treatment (for all with treatment only), age, race, intended use of sentinel node mapping, stage, histologic type, and histologic grade

Outcomes by **Diagnostic Procedure** and Treatment

| Endpoints | LEEP/Cone* | | Biopsy only | | Hazard Ratio** (95% CI) | P-value** |
|----------------------------------|---------------|-------------------|---------------|-------------------|----------------------------|-----------|
| | #Events /N | 3-year rate(%) | #Events /N | 3-year rate(%) | | |
| Pelvic or extrapelvic recurrence | | | | | | |
| • Simple Hysterectomy | 11/294 | 3.29 | 4/52 | 6.85 | 0.49 (0.15-1.60) | 0.24 |
| • Radical Hysterectomy | 7/267 | 1.63 | 3/77 | 4.33 | 0.76 (0.18-3.25) | 0.71 |
| • All with treatment | 18/561 | 2.50 | 7/129 | 5.25 | 0.59 (0.24-1.46) | 0.26 |
| Death from any cause | | | | | | |
| • Simple Hysterectomy | 6/294 | 1.09 | 1/52 | 0.00 | 1.22 (0.14-10.6) | 0.86 |
| • Radical Hysterectomy | 6/267 | 0.41 | 1/77 | 1.37 | 1.92 (0.21-17.3) | 0.56 |
| • All with treatment | 12/561 | 0.77 | 2/129 | 0.81 | 1.60 (0.34-7.41) | 0.55 |

*With or without cervical biopsy

**adjusted for treatment (for all with treatment only), age, race, intended use of sentinel node mapping, stage, histologic type, and histologic grade

Outcomes by **Residual Disease (RD)** and Treatment

| Endpoints | With RD* | | Without RD | | Hazard Ratio** (95% CI) | P-value** |
|-------------------------------|---------------|-------------------|---------------|-------------------|----------------------------|-----------|
| | #Events /N | 3-year rate(%) | #Events /N | 3-year rate(%) | | |
| Pelvic recurrence | | | | | | |
| • Simple Hysterectomy | 10/154 | 5.01 | 1/184 | 0.59 | 12.9 (1.63-102.8) | 0.02 |
| • Radical Hysterectomy | 9/163 | 3.96 | 1/181 | 0.58 | 8.09 (0.95-68.9) | 0.06 |
| • All with treatment | 19/317 | 4.46 | 2/365 | 0.59 | 11.1 (2.55-48.3) | 0.001 |
| Extrapelvic recurrence | | | | | | |
| • Simple Hysterectomy | 6/154 | 3.64 | 1/184 | 0.56 | 6.41 (0.75-54.8) | 0.09 |
| • Radical Hysterectomy | 1/163 | 0.63 | 0/181 | 0.00 | NA (0.00-NA) | 1.00 |
| • All with treatment | 7/317 | 2.07 | 1/365 | 0.28 | 8.82 (1.09-71.7) | 0.04 |

*Cervical cancer detected in hysterectomy specimen

**adjusted for treatment (for all with treatment only), age, race, intended use of sentinel node mapping, stage, histologic type, and histologic grade

Outcomes by Residual Disease (RD) and Treatment

| Endpoints | With RD* | | Without RD | | Hazard Ratio** (95% CI) | P-value** |
|----------------------------------|---------------|-------------------|---------------|-------------------|----------------------------|-----------|
| | #Events /N | 3-year rate(%) | #Events /N | 3-year rate(%) | | |
| Pelvic or extrapelvic recurrence | | | | | | |
| • Simple Hysterectomy | 13/154 | 7.14 | 2/184 | 1.15 | 7.59 (1.69-34.1) | 0.008 |
| • Radical Hysterectomy | 9/163 | 3.96 | 1/181 | 0.58 | 8.09 (0.95-68.9) | 0.06 |
| • All with treatment | 22/317 | 5.48 | 3/365 | 0.87 | 8.46 (2.50-28.7) | 0.0006 |
| Death from any cause | | | | | | |
| • Simple Hysterectomy | 6/154 | 1.44 | 1/184 | 0.56 | 6.37 (0.75-54.1) | 0.28 |
| • Radical Hysterectomy | 6/163 | 1.29 | 1/181 | 0.00 | 4.84 (0.53-44.1) | 0.16 |
| • All with treatment | 12/317 | 1.36 | 2/365 | 0.28 | 5.73 (1.25-26.2) | 0.02 |

*Cervical cancer detected in hysterectomy specimen

**adjusted for treatment (for all with treatment only), age, race, intended use of sentinel node mapping, stage, histologic type, and histologic grade